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Lower cortisol levels predict recurrence in remitted patients with recurrent depression: A 5.5 year prospective study ☆, ☆☆

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ABSTRACT

Major Depressive Disorder (MDD) is a highly recurrent disease. Stress-responsive system dysfunction seems to persist after remission. In patients with more chronic and recurrent depressive episodes, state related HPA-axis dysregulation might be a risk factor for prospective recurrence. This study examines the predictive effect of cortisol on consecutive episodes in remitted recurrently depressed patients.

Cortisol was assessed in saliva in remitted recurrently depressed patients ($n=55$) that were followed up prospectively for 5.5 years after remission. Recurrence was assessed using a well validated structured interview.

Lower mean morning cortisol levels predicted earlier time to recurrence over 5.5 year after correction for residual symptoms ($p=0.015$). Residual symptoms and childhood trauma slightly confounded the association between cortisol and recurrence. Lower cortisol levels were associated with having experienced traumatic childhood life events (42.3% in patients with lower cortisol versus 19.2% in patients with higher cortisol).

Our study provides further support for the predictive role over 5.5 year of HPA axis dysregulation, i.e. lower morning cortisol levels, of recurrence in recurrently depressed patients. Childhood trauma is associated to having lower cortisol levels. It might have long term consequences for dealing with stress and the HPA-axis.

1. Introduction

Major Depressive Disorder (MDD) is a highly recurrent disease. In the absence of prophylactic treatment, the rate of recurrence rises up to 80 percent (Frank et al.,1990). Therefore identifying predictors of recurrence and examining pathogenic mechanism of recurrence is essential. Stress has been considered as one of the cardinal pathogenic factors involved in MDD and its recurrence: childhood and recent life events, daily hassles, stress related to previous episodes and aberrant coping, all pose increased risks for MDD and its recurrences (Kessler, 1997; Kendler, Thornton, Gardner, 2001; Bockting et al., 2006a,b; Ten Doesschate et al. 2010; Nanni, Uher and Danese, 2012). Furthermore, stress reducing cognitive therapy (CT) has a benificial effect in preventing recurrence (Bockting et al., 2005, 2009; Vittengl et al., 2007; Guidi et al., 2011).

The hypothalamic pituitary adrenal (HPA) axis is the major neuroendocrine stress response system. Stress-responsive system dysfunction seems to persist after remission of acute depression. The dynamics associated with the course of the illness have not been thoroughly studied yet. Persistent dysregulation of the HPA axis after remission of depression may represent a trait-marker for the risk of recurrent depressive episodes (Modell et al., 1998, Goodyer et al., 2000; Zobel et al., 2001; Appelhof et al., 2006; Mannie et al., 2007).

Mixed findings have been reported for the role of cortisol. A previous finding of our group indicated that in remitted patients with major depression, higher posttreatment maximal cortisol levels on the DEX/CRH test were associated with relapse and with shorter relapse-free survival in a mixed outpatient group with the first and recurrent episodes (Appelhof et al., 2006). In addition, the proportion of remitted patients showing a persistent DST non-suppression were suggested to be more vulnerable to early relapse and recurrence, have poor outcome after discharge and suffer more often from persistent depression (Ribeiro et al., 1993; O'Toole and Johnson, 1997; Zobel et al., 1999). Hypercortisolism has also been reported by Zobel et al. (2001) as a marker for vulnerability for relapse and recurrence in previously depressed patients.

However, hypocortisolism has been reported as well; a phenomenon that is characterized by a hyporesponsiveness on different levels

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of the HPA axis in a number of stress-related states as Fries et al. (2005) stated in their overview. It was first reported in the eighties by using single-dose metyrapone test in depressed patients (Fava et al., 1984; Fava, 1994). Recently, Vreeburg (2010) studied in a longitudinal study including 837 patients with depressive and/or anxiety disorders, the association between salivary cortisol measures at baseline and the course of psychopathology. The patients with a lower cortisol awakening response were at a higher risk of developing a chronic course, compared to persons experiencing remission during the two-year follow up. Evening cortisol and cortisol suppression after dexamethasone intake were not associated with a chronic course. The association appeared to be similar across disorders (anxiety disorder, depressive disorder or co-morbid disorders). Another study found stable hyporeactivity of the HPA over one year in depressed women on job-stress-related long-term sick leave compared with controls (Wahlberg et al., 2009). Moreover, Sondeijker et al. (2008) reported over a study including young, not depressed adolescents, that low morning cortisol levels predicted future psychopathology.

In patients with more chronic or recurrent depressive episodes, state related HPA-axis dysregulation might be reflected in a cortisol hyposecretion when compared to non-depressed control-subjects (Oldehinkel et al., 2001). In a remitted recurrently depressed cohort of women, HPA system hypoactivity was found, both in the basal state and in response to a psychosocial stressor when compared to healthy subjects (Ahrens et al., 2008). In other disorders associated with chronic stress, such as posttraumatic stress disorder, cortisol hyposecretion has also been reported (Yehuda et al., 1990) and for a meta-analysis see (Meewisse et al., 2007). The impact of chronic stress in recurrent depression could explain why a low HPA-Axis activity could be a risk factor for recurrence.

There have been at least 361 studies performed that compared HPA axis function between depressed and non-depressed individuals, however few studies examined the predictive value of the HPA activity on course in recurrent and chronic depression (for a meta-analysis see Stetler and Miller, 2011). The current longitudinal study examined the role of the HPA axis on prospective recurrence over 5.5 years in remitted patients with recurrent depression (i.e. having at least 2 previous episodes). All patients ($N=172$) achieved a good remission state at entry of the study (i.e. not meeting criteria of a depressive episode according to the DSM-IV-TR criteria and a HRSD score less than 10), though residual symptoms are common after remission in depression (Beshai et al., 2011; Fava, 1999). Since cortisol levels are considered as rather state dependent, controlling for residual depressive symptoms in these remitted patients is necessary (Ribeiro et al., 1993). We aimed to determine (I) whether HPA-axis measures predict time to recurrence in remitted recurrently depressed patients corrected for residual depressive symptoms. In line with the previous studies on chronic recurrent depression we expect that in this *highly recurrent remitted* MDD group lower cortisol levels predict prospective recurrence over 5.5 year. Stress and childhood trauma might affect the predictive value of the HPA-axis on recurrence (Ormel et al., 2001; Carpenter et al., 2009). Therefore, (II) we will examine the role of stress (current daily hassles) and childhood trauma on the predictive value of the HPA-axis on recurrence.

2. Methods

2.1. Participants and procedure

For this study we included patients from a clinical trial in which the effect of regular care (including no care at all) on recurrence was compared to regular care with additional preventive cognitive therapy (Bockting et al., 2005). To be eligible for the trial, subjects had to meet the following criteria: (a) at least two Major Depressive Episodes (MDEs) in the last five years, as defined according to DSM-IV (1994) and assessed by the Structured Clinical Interview for DSM-IV (SCID, First et al., 1996) by trained evaluators; (b) current remission status according to DSM-IV criteria, for longer than 10 weeks and no longer than two years ago; (c) Hamilton Rating Scale for Depression (Hamilton, 1960) of <10 (as is common in relapse/recurrence prevention studies). Exclusion criteria were current mania or hypomania or a history of bipolar illness, any psychotic disorder (current and previous), organic brain damage, alcohol or drug misuse, predominant anxiety disorder, recent ECT, recent Cognitive Therapy (CT) or receiving CT at the start of the study, or current psychotherapy with a frequency of more than two times a month. Co-morbidity on axis I was assessed using the SCID (First et al., 1996). There was no restriction in using pharmacotherapy (the effect of use will be examined). Participants were recruited at psychiatric centers and through media announcement. They provided informed consent to enter the protocol. The protocol was approved by the institutional ethics review committees. We were able to collect HPA-axis baseline data from 55 patients in the control group ($N=84$; regular care only). More detail about participants, recruitment, inclusion and exclusion criteria are available in Bockting et al. (2005).

2.2. Study measures

2.2.1. Inclusion criteria and primary outcome measure

Participants were screened on inclusion and exclusion criteria via the telephone version of the Structured Clinical Interview for DSM-IV (SCID-I, APA, 1994; First et al., 1996). Kappa for interrater agreement between the interviewers (psychologist/research assistants), based on audiotaped interviews, for inclusion or exclusion was 0.77, which is indicative of good/excellent agreement. Time to recurrence was also assessed with the SCID-I (First et al., 1996). At baseline and at five follow-up assessments (3, 12, 24, 36 and 66 months), current and past depressive episodes (covering the prior months) were checked from the start of the study. All interviews were audiotaped. Two independent experienced psychiatrists who were blind to treatment condition evaluated all participants meeting the DSM-IV criteria for major depression. In cases of disagreement, the ratings of the psychiatrists were used for further analyses. The kappa for interrater agreement between the interviewers and psychiatrist on categorization of a recurrence versus no recurrence was 0.96, indicating high agreement.

2.2.2. Prediction variables

2.2.2.1. Cortisol. Salivary cortisol. Subjects were asked at baseline to provide saliva in neutral cotton salivettes (Sarstedt AG and Co, Nümbrecht, Germany) at home at three time points on two consecutive days (08:00 and 22:00, day 1, 08:00 day 2). Saliva reliably reflects the blood cortisol concentrations, in a relatively stress-free and minimally intrusive way (Kirschbaum and Hellhammer, 1994). They were instructed to rinse their mouth with water, not to brush their teeth and remain in the fasting state before collecting the sample, and to keep the samples in the refrigerator until sending the samples back to the clinic. Storage took place at −20 °C on day 3. Smoking, age, the use of antidepressants, benzodiazepines, oral contraceptives, and bodymass index were recorded. Salivary cortisol was determined by radioimmunoassay (RIA) designed for saliva samples (IBL Hamburg). The intra-assay variation for cortisol was intra- and inter-assay variations were 5.1% and 6.5%, respectively of a subsample (55 of 84 patients) hormone measures that was collected. No significant differences on any of the patient characteristics and time to recurrence were detected between this sample and the complete sample ($N=84$; all p's >0.10). The following hormone continued variables were calculated: (1) mean morning cortisol and (2) evening cortisol. Since the distributions of these measures were skewed transformed variables (by taking the natural logarithm) were used in the survival analyses.

2.2.2.2. Severity of depressive residual symptoms. The 17-item Hamilton Rating Scale for Depression (HRSD, Hamilton, 1960) was used to assess participants' baseline levels of depressive symptomatology (of <10). The HRSD, administered by psychologist/research assistants who were blind to treatment condition, is a widely used semi-structured clinical interview that covers a range of affective, behavioral and biological symptoms and has acceptable psychometric properties (Rabkin and Klein, 1987). Scores can range from 0 to 52. Our four interviewers second rated 17 interviews. The Intraclass Correlation (ICC) was 0.94, indicating high agreement. Since the distributions of these measures were skewed transformed variables (by taking the natural logarithm) were used in the survival analyses.

2.2.2.3. Stress: daily hassles en childhood trauma. To measure baseline daily hassles, the 114-item Everyday Problem Checklist was used (EPCL). The items of the EPCL refer to stressors of daily living, particularly those in the domains of work, parenthood, relationship, and household activities (continuous score). The EPCL

assesses the frequency of daily hassles over the past two months, and has good psychometric properties (Vingerhoets and van Tilburg, 1994).

We assessed childhood trauma covered 0–15 years (such as sexual abuse) with the 15-item Negative Life Events Questionnaire (dichotomized score) (Kraaij and De Wilde, 2001). This questionnaire proved to have a good predictive validity, as the number of negative life events predicted MDD-symptom severity (Kraaij et al., 2003).

2.3. Statistical analysis

The effect of cortisol on time to recurrence of a new episode was assessed with Cox regression; this takes into account differences in time at risk and censoring (no recurrence during the study period).

All analysis included the level of baseline residual symptoms (HDRS) to adjust for state effects. To examine whether the effect of HPA-measures on time to recurrence was modified by the level of residual symptoms, we first tested the interaction of cortisol (A) with residual symptoms (P); $Y=\beta_1A+\beta_2P+\beta_3AP$ assesses whether residual symptoms modifies the effect of a cortisol on time to recurrence. This is the case when the coefficient of the 2-way interaction 'cortisol by residual symptoms term' is statistically significant. If this interaction term is not significant, $Y=\beta_1A$ applies (which states that recurrence is related to cortisol).

To examine whether the effect of cortisol on time to recurrence was modified or confounded by current stress (daily hassles) and childhood trauma, a three-step procedure was used:

- *Step I:* Assesses whether either stress or childhood trauma (P) modifies the effect of cortisol (A) on recurrence (model $Y=\beta_1A+\beta_2P+\beta_3AP$, this is the case when the coefficient of the 2-way interaction cortisol by stress or childhood trauma is statistically significant).
- *Step II:* If the 2-way interaction cortisol by stress or childhood trauma interaction term in this model is not significant, potential effect modification by either stress or childhood trauma is examined (confounding effect). Following the frequently used rule of thumb the confidence intervals of the models will be compared and are considered to be different in case they differ more than 10 percent. Effect modification will be reported.
- *Step III:* If there is no effect modification, $Y=\beta_1A$ applies (which states that recurrence is related to cortisol).

To examine whether potential confounders (smoking, age, the use of antidepressants, benzodiazepines, oral contraceptives, and body mass index) confounded the association of cortisol with time to recurrence, we first examined whether the potential confounder itself predicted recurrence (alpha level of 0.10). Only in case of the variable predicted recurrence we examined further whether the effect of cortisol on time to recurrence was modified or confounded by the variable using the same procedure as described above. We used an alpha level of 0.05 for all survival analyses and 0.10 for interaction terms.

3. Results

Table 1 presents the characteristics of this patient group. As in most depression studies almost three quarter of the patients are women, 40.0% are single. The mean HRSD score is 4 with a median of 3 previous episodes. Childhood trauma was reported by 30.2% of the sample. Not all remitted patients receive treatment (34.5%), whereas 58.2% use antidepressant medication (58.8% of them use SSRI's). Benzodiazepine was used by 1 patient and no menopausal hormone treatment was reported. In this sample 29.1% used oral contraceptives.

There were no 'non-detectables' on cortisol. The detection limit was 0.40 nmol/l. Mean morning cortisol over 2 day was 20.06 nmol/l (S.D.=9.61). Mean evening cortisol over 1 day was 3.14 nmol/l (S.D.=3.46). For the analyses log transformed data were used because of skewed data. Morning cortisol (ln) on day one was highly correlated to morning cortisol (ln) on day two (Pearson correlation 0.609, $p<0.001$). There was no difference between men and women on baseline mean cortisol levels (ln): $t(53)=0.008$, $p=0.99$ (Men: $M=2.88$, S.D.=.62, Women: $M=2.88$, S.D.=.46). Baseline mean morning cortisol (ln) levels differed between baseline antidepressant users versus non-users, indicating lower baseline levels of mean morning cortisol in patients that use antidepressants: $t(53)=52.334$, $p=.029$ (AD users: $M=2.77$, S.D.=.57, Non-users: $M=3.04$, S.D.=.36). There was no significant difference between baseline evening cortisol (ln) levels and antidepressant users versus non-users, though there was a difference on the level of a trend, indicating lower baseline levels of evening cortisol in patients that use antidepressants: $t(53)=1.973$, $p=.054$ (AD users: $M=.65$, S.D.=.71, Non-users: $M=1.05$, S.D.=.77).

Table 1
Demographic and clinical characteristics.

Characteristic	(*N*=55)
Sex, female (%)	72.7
White (%)	98.0
Age (yr, mean ± S.D.)	43.8 ± 9.5
Years of education (mean ± S.D.)	14.2 ± 2.5
Single (%)	40.0
Type of current treatment (%)	
Family doctor	25.5
Psychiatric help	40.0
No treatment	34.5
Antidepressant medication (%)[a]	58.2
SSRI (%)	58.8
SNRI (%)	17.7
TCA (%)	5.9
Other (%)	11.8
HRSD-17 score (mean ± S.D.)	3.5 ± 29
Median previous episodes ± IQR[b]	3 (2–6)
Age of first onset (yr, mean ± S.D.)	27.8 ± 13.0
Co-morbid anxiety disorder (%)	10.9
Posttraumatic stress disorder (%)	0
Reported a childhood traumatic events (%)[c]	30.2
Reported general life events before 16 (%)	81.8
Daily hassles (geometric mean ± SE)[d]	3.26 ± .09
Oral contraceptives (%)	29.1
Benzodiazepines (%)	1.8
Menopausal hormone treatment (%)	0
BMI (geometric mean ± SE)[d]	3.20 ± .02
Smoking (%)	38.2
08:00 cortisol (nmol/l, mean ± S.D.)[e]	20.06 ± 9.61
22:00 cortisol (nmol/l, mean ± S.D.)	3.14 ± 3.46

[a] $n=2$ missings on type of antidepressant medication.
[b] Inter quartile range.
[c] $n=3$ missing for childhood trauma.
[d] Log transformed.
[e] Calculated mean from 2 consecutive 08:00 samples over 2 days (nmol/l, mean ± S.D.).

Relapse/recurrence

Over the 5.5 years follow-up period, 43 (78%) of our 55 participants were diagnosed with a new depressive episode. The mean time to recurrence was 668 day (Standard Error=95.96) with a median of 390 day (range: 242.39-537.61).

Comparison patients with and without a prospective recurrence

A comparison between relapsed patients versus non-relapsed patients over the 5.5 year period revealed no differences between the two groups (for evening cortisol: ($t(53)$ −0.564, $p=0.575$; for patients with a recurrence, evening cortisol (ln) $M=.8473$, S.D.=*0.7908*; for patients without a recurrence, $M=0.7073$, S.D.=0.6362); for HRSD score: ($t(53)$−1.407, $p=0.167$; for patients with a recurrence, mean HRSD score (ln) $M=2.50$, S.D.=*2.97*; for patients without a recurrence, $M=3.79$, S.D.=2.78, except for baseline mean morning cortisol levels (ln) at the level of a trend, indicating lower baseline levels of mean morning cortisol in patients that relapsed ($t(53)$ 1.940, $p=0.058$; for patients with a

recurrence, mean morning cortisol (ln) $M=2.814$, S.D.=*0.4891*; for patients without a recurrence, $M=3.126$, S.D.=0.5058).

3.1. Prediction of time to recurrence by cortisol

Mean morning cortisol predicted time to recurrence after correction for residual depressive symptoms (after correction for residual depressive symptoms: Wald(1, $N=55$)=5.889, $p=0.015$, Hazard ratio=0.442, 95% CI=0.228–0.855, without including residual symptoms: Wald(1, $N=55$) =3.374, $p=0.066$, Hazard ratio=0.554, 95% CI=0.295–1.040). Lower mean morning cortisol levels predicted earlier recurrence. Evening cortisol did not predict time to recurrence (after correction for residual depressive symptoms: Wald(1, $N=55$)=0.094, $p=0.759$, Hazard ratio=0.938, 95% CI=0.623–1.412, without including residual symptoms: Wald(1, $N=55$)=0.052, $p=0.820$, Hazard ratio=0.956, 95% CI=0.648–1.409). Both interaction terms (i.e. mean morning cortisol by residual symptoms and evening cortisol × residual symptoms) did not predict time to recurrence (both p's >1).

As presented in Table 2 none of the potential confounders (i.e. anti-depressant use, use of oral contraceptives smoking, BMI and age) was associated to time to recurrence. So we detected no moderation or confounding effect on the association between mean morning cortisol and recurrence.

3.2. Association with daily hassles and childhood life events and traumatic childhood events

Mean morning cortisol is correlated at the level of a trend with having traumatic experienced life events before the sixteenth year (mean morning cortisol (ln) dichotomized using a median split; Kappa −0.231 $p=0.071$). In the group with lower cortisol, 42.3% (11/26) experienced traumatic life events before age 16, while for the group with higher cortisol this was 19.2% (5/26).

As shown in Table 3 the number of daily hassles did not modify the association between recurrence and mean morning cortisol corrected for residual symptoms (interaction term: Wald(1, $N=55$)=2.276, $p=0.131$, Hazard ratio=.417, 95% CI=0.134–1.299). In addition, daily hassles did not confound the association between lower mean morning cortisol and earlier recurrence (adjusted hazard for cortisol; Wald(1, $N=55$)=6.546, $p=0.011$, Hazard ratio=0.418, 95% CI=0.214–0.815).

As shown in Table 3 ($n=3$ missing), having experienced *traumatic events in childhood* (for example sexual abuse) did not modify the association between recurrence and mean morning cortisol corrected for residual symptoms (interaction term: Wald(1, $N=52$)=1.77, $p=0.674$, Hazard ratio=1.165, 95% CI=0.571–2.376). It did however confound this association (>10% change of confidence intervals of cortisol including childhood trauma in the model): including childhood trauma Wald(1, $N=52$)=3.641, $p=.056$, Hazard ratio=0.512, 95% CI=0.258–1.018 versus 95% CI without childhood trauma: Wald(1, $N=52$)=5.789, $p=0.016$, Hazard ratio=0.439, 95% CI=0.224–0.858. An exploratory multivariate analysis including mean morning cortisol, daily hassles and childhood trauma (after correction for residual symptoms) revealed that all variables independently (interaction terms could not be tested) predict time to recurrence ($n=52$, $n=3$ is missing: for total model $p=0.001$, for mean morning cortisol $p=0.051$, for childhood trauma, $p=0.024$ and for daily hassles $p=0.055$).

Table 2
Potential confounders of the association between mean morning cortisol and recurrence* ($N=55$).

Predictor[a] Univariate prediction of relapse		Mean morning cortisol	Anti-depressant use	Contraceptive use	Smoking	Body Mass Index (BMI)	Age
	Wald	5.889	0.018	1.723	0.034	1.138	0.079
	β	−0.817	−0.042	−0.428	0.059	−0.906	−0.005
	Exp(β)	0.442	0.59	0.652	1.061	0.404	0.995
	P	0.015	0.892	0.189	0.853	0.286	0.779
	CI	0.228–0.855	0.522–1.762	0.344–1.235	0.568–1.979	0.077–2.135	0.961–1.030

* All models corrected for residual symptoms.
[a] Continuous variables: mean morning cortisol, residual symptoms, age, BMI (all log transformed because of skewness), all the other variables were dichotomous.

Table 3
Role of stress and childhood trauma on the association between mean morning cortisol and recurrence ($N=55$).

Variable[a]		**Model 1**[b]	**Model 2**		**Model 3**
		Potential confounder by mean morning cortisol interaction	Potential confounder	Mean morning cortisol	Mean morning cortisol
Daily hassles	Wald	2.276	3.748	6.546	5.889
	β	−0.874	0.466	−0.872	−0.817
	Exp(β)	0.417	1.594	0.418	0.442
	P	0.131	0.053	0.011	0.015
	CI	0.134–1.299	0.994–2.555	0.214–0.815	0.228–0.855
Childhood traumatic events*	Wald	0.177	4.939	3.641	5.789
	β	0.153	0.392	−0.669	−0.824
	Exp(β)	1.165	1.480	0.512	0.439
	P	0.674	0.026	0.056	0.016
	CI	0.571–2.376	1.047–2.091	*0.258–1.018***	0.224–0.858

[a] Continuous variables: mean morning cortisol, residual symptoms, daily hassles (all log transformed because of skewness), dichotomous: Childhood trauma.
[b] Model I: ln mean morning cortisol by potential confounder interaction, corrected for residual symptoms. Model II: ln mean morning cortisol, potential confounder corrected for residual symptoms. Model III: ln mean morning cortisol corrected for residual symptoms.
* $n=3$ missing.
** Confounding effect for traumatic childhood events trauma.

4. Discussion

We examined the predictive value of HPA-axis over 5.5 years in patients with remitted recurrent depression. In line with our expectation we found that relatively lower mean morning cortisol levels predicted *within this patient group*, earlier time to recurrence over this 5.5-year period, while evening cortisol did not predict time recurrence. A multivariate analyses revealed that mean morning cortisol, childhood trauma and daily hassles tend to be independently associated to recurrence. However, interaction terms in this multivariate model could not be tested given the relatively small sample ($n=55$). Though childhood trauma slightly confounded the prediction of recurrence by mean morning cortisol. This supports prior findings that chronicity and recurrence in depression is associated with lower levels of cortisol (Oldehinkel et al., 2001; Ahrens et al., 2008; Vreeburg, 2010). Ahrens et al. (2008) reported hypoactivity over a remitted recurrently depressed cohort with exclusively women. We found no significant differences in mean morning cortisol levels between men and women.

The impact of stress in recurrent depression could explain why a relatively low HPA-Axis activity is a risk factor for recurrence in recurrent depression. In recurrent depression daily hassles and life events seem to predict subsequent recurrence (Ormel et al., 2001; Bockting et al., 2006a,b). Daily hassles and life events may result in states of chronic stress exposure which may cause an allostatic load, i.e., fluctuation and heightened neural or endocrine response, as pointed out by Fava (1999).

Having experienced traumatic events in childhood might have a crucial role in the HPA-axis, in dealing with stress and subsequently in onset and course of depression (chronicity). Childhood traumas have been reported before as an independent determinant of chronicity of depression (Wiersma et al., 2009). This is in line with our finding that lower cortisol levels within this patient group were associated to having experienced more traumatic life events in childhood and predicted prospective recurrence (42.3% of the patients with lower cortisol experienced traumatic life events while 19.2% experienced childhood trauma in patients with higher cortisol). Treadway et al. (2009) suggest that chronic stress subsequent to childhood maltreatment may serve to initiate glucocorticoid-related injury to the anterior cingulate cortex. This damage may impair cortico-limbic circuits involved in emotion regulation.

Carpenter and colleagues reported that especially emotional childhood abuse might dampen cortisol reactivity that is cumulative overtime (Carpenter et al., 2009), which has been shown in a study amongst 230 adults without major Axis I Disorders that completed the Dex/CRH test. Unfortunately, we do not have data on emotional abuse in childhood to examine this hypothesis. However, we did indeed find an indication that childhood trauma in general (such as sexual abuse) slightly confounded the prediction of recurrence by mean morning cortisol.

Miller et al. (2007) showed in their meta-analysis on the impact of chronic stress on HPA function that much of the variability in HPA response is attributable to stressor features. Timing is a critical element, as hormonal activity is elevated at stress onset but reduced as time passes. Stress that threatens physical integrity is traumatic in nature, and is largely uncontrollable that elicits a high, flat diurnal profile of cortisol secretion. Together, this can result in poor regulation of stress, and could play a role in both the initiation of depression and increased vulnerability to recurrence. Alternatively, lowered cortisol levels in the remitted state may reflect a direct biological vulnerability for recurrent depressive episodes which, consequently, heightens the impact of daily hassles in these patients. To explain our findings, one might hypothesize that during the course of recurrent depression, an initial HPA overdrive may lead to increased basal cortisol levels associated with an abrupt stress response, and after remission of depression, may be followed by a dampened/muted basal as well as stress-induced HPA activity.

Alternatively, our findings if replicated might indicate the hypothetical existence of different depression phenotypes (Bouhuys et al., 2006). One type may be characterized by normalization of HPA system function or even by evolving HPA hypo-activity associated with stable remission. Another type may show sustained HPA system dysfunction after remission as well as an increased risk for recurrence. One might speculate that our group of remitted patients included more subjects from the second group, giving insight in stress system regulation in this subtype.

Besides antidepressant medication, psychological interventions in the maintenance phase, such as brief cognitive therapy either added to regular care or medication, and Mindfulness-Based Cognitive therapy, are helpful in preventing relapse/recurrence (Bockting et al., 2005, 2009; Vittengl et al., 2007; Guidi et al., 2011). As previously reported (Bockting et al., 2006a,b) in patients who received additional preventive cognitive therapy, cortisol levels did not predict time to relapse. Possibly in patients who were treated with psychological preventive interventions, the impact of daily hassles on recurrence is reduced, and therefore the extent to which patterns of depressive thinking were reactivated is limited, resulting in the absence of lowered cortisol as a risk factor for recurrence.

This study contains strengths and weaknesses. Strengths of the study are the fact that our cohort included exclusively patients with at least two previous episodes and was followed prospectively for 5.5 years. Further, we included patients with recurrent depression remitted on variety of treatments or no treatment at all, without restrictions on medication status at entry to the study. As such, this study was designed to maximize external validity, which suggests good generalizability of the findings. However, there are also several limitations to address. First, the relatively small sample size reducing the power to detect weaker associations between recurrence and the interaction between cortisol, daily stress and experienced childhood trauma. However, longitudinal studies in this high risk group for recurrence (i.e. patients with recurrent depression) are scarce. Second, we have no data on waking time and sleep quality of the subjects. Third, we only measured one morning concentration (mean of 2 day morning assessments) instead of the whole cortisol awakening response, and so based our cortisol course over the day estimation on two measurements. However, all our effects were estimated on values measured using identical methodology. Fourth, our results restrict to prediction of recurrence within this sample and does not include a comparison to a normal control group. Fifth, this sample included a mixed group of patients that used antidepressants and patients that did not use this. In line with other studies (Holsboer and Barden, 1996; Michelson et al., 1997; Deuschle et al., 2003; Vreeburg et al., 2009; Manthey et al., 2011), we found an association between use of antidepressants and decreased cortisol levels. However, in line with Vreeburg et al.'s (2009) findings were comparable after controlling for the confounding effect of use of antidepressants. Finally, we assessed childhood trauma by using a self-report questionnaire rather than an interview. This might underscore the actual prevalence of childhood trauma.

In sum, our study adds further support for the predictive role of HPA axis dysregulation, i.e. lower morning cortisol levels, in relapse and recurrence of recurrent depression. This effect could not be explained by state dependent depressive residual symptoms, though residual symptoms slightly confounded the association.

Childhood traumatic life events might have an impact on the HPA-axis and thereby on the impact of stress as risk factor for recurrence in depression. Replication is necessary to confirm the impact of childhood traumatic life events on the HPA-axis and thereby on prospective recurrence. Future studies are needed to examine this specific pathogenic role of cortisol in interaction with stress and childhood trauma as risk factor for recurrence

in larger longitudinal samples in this chronic highly recurrent disease.

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References

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4rd ed (DSM-IV), Washington, DC, APA.

Ahrens, T., Deuschle, M., Krumm, B., van der Pompe, G., den Boer, J.A., Lederbogen, F., 2008. Pituitary-adrenal and sympathetic nervous system responses to stress in women remitted from recurrent major depression. Psychosomatic Medicine 70, 461–467.

Appelhof, B.C., Huyser, J., Verwey, M., Brouwer, J.P., Dyck, R., van., Fliers, E., Witte Hoogendijk, J.G., Tijssen, J.G.P., Wiersinga, W.M., Schene, A.H., 2006. Glucocorticoids and relapse of major depression (dexamethasone/corticotropin-releasing hormone test in relation to relapse of major depression). Biological Psychiatry 59, 696–701.

Beshai, S., Dobson, K.S., Bockting, C.L.H., Quigley, L., 2011. Relapse and recurrence prevention in depression. Current research and future prospects. Clinical Psychology Review 31 (8), 1349–1360.

Bockting, C.L.H., Schene, A.H., Spinhoven, Ph., Koeter, M.W.J., Wouters, L.F., Huyser, J., Kamphuis, J.H., 2005. Preventing relapse/recurrence in recurrent depression using cognitive therapy. Journal of Consulting and Clinical Psychology 73, 647–657.

Bockting, C.L.H., Spinhoven, P., Koeter, M.W., Wouters, L.F., Schene, A.H., 2006a. Prediction of recurrence in recurrent depression and the influence of consecutive episodes on vulnerability for depression: a 2-year prospective study. Journal of Clinical Psychiatry 67, 747–755.

Bockting, C.L.H., Spinhoven, Ph., Koeter, M.W.J., Wouters, L.F., Visser, I., Schene, A.H., 2006b. Differential predictors of response to preventive cognitive therapy in recurrent depression: a 2-year prospective study. Psychotherapy and Psychosomatics 75, 229–236.

Bockting, C.L.H., Spinhoven, Ph., Wouters, L.K., Koeter, M.W.J., Schene, A.H., 2009. Long term effects of preventive cognitive therapy in recurrent depression using: 5.5 years follow-up. Journal of Clinical Psychiatry 70, 1621–1628.

Bouhuys, A.L., Bos, E.H., Geerts, E., van Os, T.W., Ormel, J., 2006. The association between levels of cortisol secretion and fear perception in patients with remitted depression predicts recurrence. The Journal of Nervous and Mental Disease 194, 478–484.

Carpenter, L.L., Tyrka, A.R., Ross, N.S., Khoury, L., Anderson, G.M., Price, L.H., 2009. Effect of childhood emotional abuse and age on cortisol responsivity in adulthood. Biological Psychiatry 66, 69–75.

Deuschle, M., Hamann, B., Meichel, C., Krumm, B., Lederbogen, F., Kniest, A., Colla, M., Heuser, I., 2003. Antidepressive treatment with amitriptyline and paroxetine: effects on saliva cortisol concentrations. Journal of Clinical Psychopharmacology 23, 201–205.

Fava, G.A., Carson, S.W., Perini, G.I., Morphy, M.A., Molnar, G., Jusko, W.J., 1984. The metyrapone test in affective disorders and schizophrenia. Journal of Affective Disorders 6, 241–247.

Fava, G.A., 1994. Affective disorders and endocrine disease. New insights from psychosomatic studies. Psychosomatics 35, 341–353.

Fava, G.A., 1999. Subclinical symptoms in mood disorders: pathophysiological and therapeutic implications. Psychological Medicine 29, 47–61.

First, M.B., Gibbon, M., Spitzer, R.L., Williams, J.B., 1996. User Guide for the Structured Clinical Interview for DSM-IV Axis 1 Disorders. American Psychiatric Association, Washington, DC.

Frank, E., Kupfer, D.J., Perel, J.M., Cornes, C., Jarret, J.B., Mallinger, A.G., Thase, M.E., McEachran, A.B., Grochocinski, V.J., 1990. Three-year outcomes for maintenance therapies in recurrent depression. Archives of General Psychiatry 47, 1093–1099.

Fries, E., Hesse, J., Hellhammer, J., Hellhammer, D.H., 2005. A new view on hypocortisolism. Psychoneuroendocrinology 30, 1010–1016.

Goodyer, I.M., Herbert, J., Tamplin, A., Altham, P.M., 2000. First-episode major depression in adolescents. Affective, cognitive and endocrine characteristics of risk status and predictors of onset. British Journal of Psychiatry 176, 142–149.

Guidi, J., Fava, G.A., Fava, M., Papakostas, G.I., 2011. Efficacy of the sequential integration of psychotherapy and pharmacotherapy in major depressive disorder: a preliminary meta-analysis. Psychological Medicine 41, 321–331.

Hamilton, M., 1960. A rating scale for depression. Journal of Neurology, Neurosurgery and Psychiatry 23, 6–62.

Holsboer, F., Barden, N., 1996. Antidepressants and hypothalamic-pituitary-adrenocortical regulation. Endocrinology Review 17, 187–205.

Kendler, K.S., Thornton, L.M., Gardner, C.O., 2001. Genetic risk, number of previous depressive episodes, and stressful life events in predicting onset of major depression. American Journal of Psychiatry 158, 582–586.

Kessler, R.C., 1997. The effects of stressful life events on depression. Annual Review of Psychology 48, 191–214.

Kirschbaum, C., Hellhammer, D.H., 1994. Salivary cortisol in psychoneuroendocrine research: recent developments and applications. Psychoneuroendocrinology 19, 313–333.

Kraaij, V., De Wilde, E.J., 2001. Negative life events and depressive symptoms in the elderly: a life span perspective. Aging and Mental Health 5, 84–91.

Kraaij, V., Garnefski, N., de Wilde, E.J., Dijkstra, A., Gebhardt, W., Maes, S., et al., 2003. Negative life events and depressive symptoms in late adolescence: bonding and cognitive coping as vulnerability factors? Journal of Youth and Adolescence 185–193.

Mannie, Z.N., Harmer, C.J., Cowen, P.J., 2007. Increased waking salivary cortisol levels in young people at familial risk of depression. American Journal of Psychiatry 164, 617–621.

Manthey, L., Leeds, C., Giltay, E.J., van Veen, T., Vreeburg, S.A., Penninx, B.W., Zitman, F.G., 2011. Antidepressant use and salivary cortisol in depressive and anxiety disorders. European Neuropsychopharmacology.

Meewisse, M.L., Reitsma, J.B., de Vries, G.J., Gersons, B.P., Olff, M., 2007. Cortisol and post-traumatic stress disorder in adults: systematic review and meta-analysis. British Journal of Psychiatry 191, 387–392.

Michelson, D., Galliven, E., Hill, L., Demitrack, M., Chrousos, G., Gold, P., 1997. Chronic imipramine is associated with diminished hypothalamic-pituitary-adrenal axis responsivity in healthy humans. Journal of Clinical Endocrinology and Metabolism 82, 2601–2606.

Miller, G.E., Chen, E., Zhou, E.S., 2007. If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychological Bulletin 133, 25–45.

Modell, S., Lauer, C.J., Schreiber, W., Huber, J., Krieg, J.C., Holsboer, F., 1998. Hormonal response pattern in the combined DEX-CRH test is stable over time in subjects at high familial risk for affective disorders. Neuropsychopharmacology 18, 253–262.

Nanni, V., Uher, R., Danese, A., 2012. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. American Journal of Psychiatry 169, 141–151.

Oldehinkel, A.J., van den Berg, M.D., Flentge, F., Bouhuys, A.L., ter Horst, G.J., Ormel, J., 2001. Urinary free cortisol excretion in elderly persons with minor and major depression. Psychiatry Research 104, 39–47.

Ormel, J., Oldehinkel, A.J., Brilman, E.I., 2001. The interplay and etiological continuity of neuroticism, difficulties, and life events in the etiology of major and subsyndromal, first and recurrent depressive episodes in later life. American Journal of Psychiatry 158, 885–891.

O'Toole, S.M., Johnson, D.A., 1997. Psychobiology and psychopharmacotherapy of unipolar major depression: a review. Archives of Psychiatric Nursing 11, 304–313.

Rabkin, J.G., Klein, D.F., 1987. The clinical measurement of depressive disorders. In: Marsella, A., Hirschfeld, R., Katz, M. (Eds.), The Measurement of Depression. Guilford Press, New York, pp. 30–83.

Ribeiro, S.C., Tandon, R., Grunhaus, L., Greden, J.F., 1993. The DST as a predictor of outcome in depression: a meta-analysis. American Journal of Psychiatry 150, 1618–1629.

Sondeijker, F.E., Ferdinand, R.F., Oldehinkel, A.J., Tiemeier, H., Ormel, J., Verhulst, F.C., 2008. HPA-axis activity as a predictor of future disruptive behaviors in young adolescents. Psychophysiology 45, 398–404.

Stetler, C., Miller, G.E., 2011. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. Psychosomatic Medicine 73, 114–126.

Ten Doesschate, M.C., Bockting, C.L.H., Koeter, M.W.J., Schene, A.H., 2010. Prediction of recurrence in recurrent depression: a 5.5-year prospective study. Journal of Clinical Psychiatry 71, 984–991.

Treadway, M.T., Grant, M.M., Ding, Z., Hollon, S.D., Gore, J.C., Shelton, R.C., 2009. Early adverse events, HPA activity and rostral anterior cingulate volume in MDD. PLoS One 4, e4887.

Vingerhoets, A.J.J.M., van Tilburg, M.A.L., 1994. Everyday Problem Checklist (EPCL). Lisse, Swets & Zeitlinger.

Vittengl, J.R., Clark, L.A., Dunn, T.W., Jarrett, R.B., 2007. Reducing relapse and recurrence in unipolar depression: a comparative meta-analysis of cognitive-behavioral therapy's effects. Journal of Consulting and Clinical Psychology 75, 475–488.

Vreeburg, S.A., 2010. Hypothalamic–Pituitary–Adrenal Axis Activity in Depressive and Anxiety Disorders. Dissertation. Vrije Universiteit, Amsterdam (Chapter 7).

Vreeburg, S.A., Hoogendijk, W.J., van Pelt, J., Derijk, R.H., Verhagen, J.C., van Dyck, R., Smit, J.H., Zitman, F.G., Penninx, B.W., 2009. Major depressive disorder and hypothalamic–pituitary–adrenal axis activity: results from a large cohort study. Archives of General Psychiatry 66, 617–626.

Wahlberg, K., Ghatan, P.H., Modell, S., Nygre, A., Ingvar, M., Asber, M., Heilig, M., 2009. Suppressed neuroendocrine stress response in depressed women on job-stress-related long-term sick leave: a stable marker potentially suggestive of preexisting vulnerability. Biological Psychiatry 65, 742–747.

Wiersma, J.E., Hovens, J.G., van Oppen, P., Giltay, E.J., van Schaik, D.J., Beekman, A.T., Penninx, B.W., 2009. The importance of childhood trauma and childhood life events for chronicity of depression in adults. Journal of Clinical Psychiatry 70, 983–989.

Yehuda, R., Southwick, S.M., Nussbaum, G., Wahby, V., Giller Jr., E.L., Mason, J.W., 1990. Low urinary cortisol excretion in patients with posttraumatic stress disorder. The Journal of Nervous and Mental Disease 178, 366–369.

Zobel, A.W., Yassouridis, A., Frieboes, R.M., Holsboer, F., 1999. Prediction of medium-term outcome by cortisol response to the combined dexamethasone-CRH test in patients with remitted depression. American Journal of Psychiatry 156, 949–951.

Zobel, A.W., Nickel, T., Sonntag, A., Uhr, M., Holsboer, F., Ising, M., 2001. Cortisol response in the combined dexamethasone/CRH test as predictor of relapse in patients with remitted depression. a prospective study. Journal of Psychiatry Research 35, 83–94.